specificity *in vitro* cannot alone support the predictability of the method for prevention of or treating said tumor growth through administration of the antibody.

Applicants submit that the presently claimed methods are enabled by the specification as filed. The specification describes formulations containing an antibody that binds HER2 receptor. Specifically exemplified is the formulation of the humanized antibody huMAb4D5-8 (HERCEPTIN®). See page 25, lines 13-18 of the application. The HERCEPTIN® antibody has received marketing approval for treatment of patients with metastatic breast cancer whose tumors overexpress the HER2 protein. See HERCEPTIN® (Trastuzumab) Product Information (2000) (of record - item no. 243 of the IDS filed 12/27/00).

The present application describes a formulation which is particularly adapted for subcutaneous administration and comprises an antibody that binds HER2 receptor (see claims 42 and 48; and page 2, lines 16-18). The formulation, in at least one embodiment of the invention, comprises an antibody which binds HER2 receptor in an amount of about 50mg/mL to about 400mg/mL (claims 43 and 47). The present application points out that the delivery of high protein concentration is often required for subcutaneous administration due to the volume limitations (≤ 1.5 mL) and dosing requirements (≥ 100mg). See page 29, lines 8-9 of the application. The present application describes how to overcome the problems associated with obtaining such high antibody concentrations in the formulation (page 29, lines 9-15), thus allowing for subcutaneous administration of the antibody in the formulation.

Aside from therapy of breast cancer noted above, the specification identifies other cancers characterized by overexpression of HER2

receptor. For example, ovarian, stomach, endometrial, salivary gland, lung, kidney, colon and bladder cancer are identified on page 24, lines 11-14 of the application. Applicants submit that based on the teachings of the present application combined with the level of skill in the art at the filing date, the skilled clinician could have treated cancers, in addition to breast cancer discussed above. For instance, Applicants draw the Examiner's attention to the enclosed copies of Ohnishi *et al. British Journal of Cancer (Scotland)* 71(5):969-973 (1995) and Tokuda *et al. British Journal of Cancer (Scotland)* 73(11):1362-1365 (1996), describing therapy of stomach/gastric cancer with antibodies that bind HER2 receptor; and Kern *et al. Am. J. Resp. Cell. & Molec. Biol.* 9:448-454 (1993), which reports therapy of lung cancer with an antibody that binds HER2 receptor. Hence, Applicants submit that the present application enables treating a mammal with a cancer characterized by overexpression of HER2 receptor.

With regard to therapy with antibodies other than huMAb4D5-8 (HERCEPTIN®) exemplified, Applicants direct the Examiner's attention to US Patent No. 5,725,856, Hudziak *et al.* (of record, hereinafter "the '856 patent") which disclosed high affinity anti-HER2 antibodies 4D5, 3E8 and 3H4 that significantly inhibited the growth of cancer cells that overexpress HER2 (see, *e.g.* column 18, lines 13-19 and Figure 3). The '856 patent further described that high affinity anti-HER2 antibodies can inhibit tumor growth *in vivo* (see, *e.g.* Table 2 in column 19 which discloses the *in vivo* activity of Mabs 2H11 and 3E8). Other therapeutically effective antibodies that bound HER2 receptor were also described in the art prior to the filing of the above application. This is supported, for instance, in Table 1 of Hudziak *et al. Molec. & Cell. Biol.* 9(3):1165-1172 (1989) (of record) which describes further high affinity, therapeutically useful antibodies (*e.g.* 7C2, 2C4 and

7F3). In addition, Applicants direct the Examiner's attention to US Patent No. 5,821,337, Carter *et al.* (of record, hereinafter "the '337 patent"), which describes humanized antibodies in addition to huMAb4D5-8 (HERCEPTIN®) which could be used for therapy. See, especially, Example 1 on columns 48-55 and Example 3 on columns 58-64. Thus, these humanized antibodies available at the time of filing the present application could also have been used for the presently claimed therapeutic methods. Aside from humanized antibodies, human antibodies that bind HER2 receptor were also available for use in the methods claimed herein. See, for example, US Patent No. 6,165,464, copy attached.

As to subcutaneous administration of the antibody (as claimed in claims 42 and 48), versus intravenous administration, Applicants attach a copy of a poster presented by Combs *et al.* at the *AAPS National Meeting* in 1999 entitled "Comparative Efficacy of HERCEPTIN® in the Nude Mouse Tumor Xenograft Model: IV Bolus Versus Subcutaneous Infusion". This poster demonstrates that subcutaneous administration of the antibody which binds HER2 receptor as described in the present application (*e.g.* at page 24, lines 11-16) inhibits tumor growth of cancer cells overexpressing the HER2 receptor *in vivo*.

Thus Applicants submit that the present application does teach how to treat a mammal with a cancer characterized by overexpression of HER2 receptor as set forth in the pending claims. Reconsideration and withdrawal of the Section 112, first paragraph rejection is respectfully requested in view of the above.

Information Disclosure Statements

Applicants note that refs. 38-53 of the PTO-1449 form submitted with the IDS filed with the initial application have not been

initialed by the Examiner. Applicants assume that the Examiner has access to references 38-53 and would appreciate it if she could return an initialed copy of this page of the PTO-1449 form indicating that these references have been considered with respect to the above application.

In addition, Applicants do not have confirmation that references 59-61 of the Supplemental IDS filed 7/14/99 were considered and would appreciate it if the Examiner could return a copy of the initialed PTO-1449 form confirming consideration of these references.

Finally, a further Supplemental IDS was filed 12/27/00 and an additional Supplemental IDS is submitted herewith. Reconsideration of these additional references is respectfully requested.

Applicants believe that this application is now in order for allowance and look forward to early notification to that effect. In the event however, that there are outstanding issues to be resolved, the Examiner is invited to call the undersigned to discuss these.

Respectfully submitted,

GENENTECH, INC.

Date: February 28, 2001

By: _____

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